

**Feasibility of Integrating Pharmacogenomics into Drug  
Development from an Economic Perspective**

*Thomas A. Metcalfe*

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DR. WINN-DEEN: So now, Pharmacogenomics, Part 2.

It is my pleasure to introduce our first speaker of the next session, Tom Metcalfe. He is the head of the biomarker program for Roche Pharma. Tom has the unique perspective of also having worked on the diagnostic side of the Roche organization, and he is going to talk to us a little bit about how Roche as an exemplar pharma company is using biomarkers in their drug development process.

Tom, you can sit there if you want, or would you rather come up?

MR. METCALFE: I prefer to come up there.

DR. WINN-DEEN: You're actually much less intimidating if you sit down.

(Laughter.)

DR. WINN-DEEN: I should disclose that I used to work for Tom, and we were quite a pair when we went out in public together.

MR. METCALFE: Sorry if this is intimidating for you, but this is usual for me. So thank you to the committee for the opportunity to present to you on this topic.

As Emily said, my comments today are based principally on Roche's experiences in this field, but we believe that much of our experience is relevant to the pharmaceutical and diagnostics industry in general.

What I'm particularly going to talk about is some of the process aspects, and I'll really then tease out the feasibility of integrating pharmacogenetics and biomarkers into drug development from an economic perspective.

I think this broad definition of biomarkers is an objective measure or evaluation of normal biological processes, pathogenic processes, pharmacologic responses to a therapeutic intervention, or responses to preventative or other health care interventions generally broadly expected or broadly accepted.

Obviously as a part of that, biomarkers can increase our understanding of drug metabolism, drug action, efficacy, safety, facilitate therapy response-prediction, and expand the molecular definition of disease and inform about the course of disease progression.

Obviously this broad definition includes all diagnostic tests, imaging technologies, and other subjective measures of a person's health status, and obviously all pharmacodiagnostic tests. Most of my remarks are going to be focused on novel markers, either newly discovered markers, or markers which are being validated for novel applications.

So just a little bit about what's new, what's changing. Obviously genetics, genomics, proteomics, modern imaging techniques under the technologies allow us to measure many more markers than we could before. There is an improved understanding of the targets of pharmaceutical

interventions, signaling pathways, metabolism, and mechanism of toxicity, and this will allow us to make more sense of the biomarker data that we're looking at, and biostatistics and bioinformatics allowing us to collect, store, and interpret this data more effectively.

Nonetheless, there is a tidal wave of data which we are generating, and it takes a lot of time and energy to interpret this effectively.

So again, how is this affecting pharmaceutical development, and particularly the integration of biomarkers and pharmacodiagnosics into drug development? These new marker data are allowing us to make considerably richer decisions in late research and early development. This is about which projects to move forward, and what the comparative, I suppose, prospects of different molecules in the pipeline are, but this is essentially an evolution of what we currently do with pharmacogenomic and pharmacogenetic markers.

Unfortunately, there is yet as few validated surrogate markers which allow us to run considerably short at trials. I think quite rightly, the status of a surrogate marker for a clinical endpoint is set very high, and there is a lot of evidence needed for us to reach the status of a validated surrogate. This will mean that it is going to take some time until we get considerably more surrogate markers and are able therefore to run shorter trials.

There are also as of yet very few highly informative response markers which allow us to run smaller trials or enrich our trials to potential responders. So we see this as being a steady evolution of the drug development process rather than a revolution, particularly because the first part is an evolution of the current paradigm, and we have few examples of predictive markers and of surrogate markers.

The various utilities that we see for biomarkers and novel genomic/genetic markers in drug development are pharmacodynamic markers which confirm biological activity, enable us to make early decisions on progressing molecules, and make optimization of dosing and scheduling more efficient, prognostic markers which correlate with disease outcome, and these enable or improve our ability to design informative trials and to interpret these trials competently.

Disease-specific markers which correlate well with the presence or absence of a disease. In some cases, these can be used to identify disease subtypes that are more amenable to one therapeutic intervention than to another, and can be used to enrich our trials for those most likely to respond. I think this is a very useful utility which we are beginning to use more. As you can see, this is not directly related to the action, efficacy, or safety of a particular drug. These are disease-specific markers.

The last category are predictive markers, such as HER2 overexpression in breast cancer, which correlate strongly with the activity of our drugs. Depending on how strong this is, we can include this in our trial design.

So this could lead us to come up with one possible classification of novel biomarkers with disease markers, pharmacological markers, and predictive pharmacodiagnosics set out like this. Obviously there is an overlap between these different sets. Some of the disease markers are predictive pharmacodiagnosics, as with HER2, but many are not.

I think it's very important that we begin to tease apart these different utilities and whether or not a disease marker can be used as a predictor pharmacodiagnostic. In our experience, in many cases these disease biomarkers lack the specificity to be used as predictive pharmacodiagnosics.

So I'm going to focus most of what I talk about about predictive pharmacodiagnostics, and especially with relation to the impacts on the economics of drug development.

Pharmacodynamic and prognostic tests tend to increase the value, or if you integrate them into drug development, they tend to increase the value of that drug development principally because the size of the market that you're addressing is not really affected, revenues do not decrease, and they may increase because we can improve dosing and dose scheduling, and investments in markers generally are offset by improved decisionmaking, trial design, reduced attrition, and therefore beneficial in general.

I don't think pharma companies have any issues at all including this work in theirs, or these sorts of markers in their drug development work, because it's generally beneficial.

The value impact of predictive markers is less clear. They may reduce the size of the market. This reduction in the size of the market may be offset by improvements in market penetration, increased average duration of therapy, and potentially in pricing. I think the pricing point is what we need to look at, because obviously this is only relevant if this is done before the pricing is set within the market. It may also improve the competitive position of the drug. But I think the most critical thing about this is it depends upon exactly what we're looking at, and it requires careful case by case analysis.

I'll take you through some of the analytical components later on to show you the complexity of it.

Now, looking particularly at the application for response prediction, this is a prototypic concept for the application of these sorts of markers, and it is schematic, but I think it also teaches us some important lessons.

The first thing that one has to do if one is going to include response markers in a drug development program is to have a reliable understanding of first of all, the biology of the marker, and then also the test that one is using to test for that marker.

So we generally have to spend considerable time in early drug development and biomarker discovery, and then work up those biomarkers into reliable tests, invest time in biomarker test development and validation, and then as we start introducing the drug, to collect samples and store those samples.

The most informative time in early development is going to be Phase 2, because in general, Phase 1, or in early clinical development, there is a lack of conclusions that one can draw. One generally begins to be able to draw conclusions about whether or not a drug is working or not at the end of Phase 2.

So if one knows which biomarkers one wants to look at, has been able to develop a test, then it's possible to do a retrospective analysis of these biomarkers on samples collected in Phase 2 and correlate these with response, or lack thereof, or perhaps with safety as well.

One possible thing one could do is prospectively recruit the patients using biomarkers found to be useful at the end of Phase 2 in your Phase 3 program. But in order to do this, you'd have to have a very informative and reliable biomarker. In general, we find that it's very difficult to find biomarkers which are informative enough to have us take the risk of recruiting for a Phase 3 trial based on a response marker.

An alternative to this might be to balance the various arms of a trial to make sure that both arms are equally populated with patients who have a good chance of response using this marker. So this is I think one way of doing things, but currently we rarely run into the situation where we can do this at the moment. This means that we are therefore essentially not changing how we develop drugs. We are tracking more things, but we are not changing the trial protocols as yet, or in very few cases.

I think the one drug where this paradigm was followed was with Herceptin. This is the current diagnostic paradigm that is used to determine whether or not the patient is eligible for Herceptin therapy. There are two particular tests which are used. One is immunohistochemistry, which is basically testing a patient's tumor tissue, then if he has a result which needs further interpretation, one applies what is called a FISH test to that patient as well.

So that worked with Herceptin therapy. One of the reasons that worked was because the marker was informative enough. But now I'm going to sort of come onto some questions which arise if one wants to apply this paradigm broadly.

First is what is an acceptable response rate for a novel drug? One should think about applying a stratification with a response marker. If you go towards the end of this scale where you have a very low response rate, the first thing you start to question is whether or not you have a viable drug. It is only when you move up perhaps above the 10 percent response rate that you think maybe you could apply a response marker in your clinical development.

When you get above the 50, 60, 70 percent in terms of response, this is an excellent response for a novel drug. Again, you start beginning to think whether or not it makes sense to apply a response marker. So clearly there is some window of opportunity, and many drugs do fall into this category. But I think that's one set of questions which one has to ask.

The second set of questions which one has to ask is whether or not you're looking at response, or whether you're looking at safety markers. Clearly we believe that when you look at the balance between increasing efficacy of a drug and increasing safety of a drug, it is much more likely that we're going to be using this initially to be increasing safety of a drug simply because of the practical issues of predicting adverse events reliably. This is in terms of predicting adverse events. I think it's different if you're monitoring potential adverse events. But for predicting adverse events, it becomes very difficult, because these are likely to be infrequent events with a useful drug.

The third thing that one has to take into account is what particular indication you are looking at, and also what the balance is between efficacy and risk in that indication. Clearly in indications like cancer, there is a high utility of this sort of approach, because patients have a very great medical need, and one is prepared to take on perhaps more safety issues because of potential benefits than one would in other indications.

A second set of issues that one runs into when you are looking at this is defining what you call response. As I said at the end of Phase 2, you're looking for responders, and you're looking to correlate these markers with responders. If you don't have a clear idea about what a responder is and what a response phenotype is, you can run into issues.

A recent example that we've run into is looking at patients suffering from rheumatoid arthritis where there are two accepted or broadly accepted, the ACR is the most accepted test of whether or not a patient is responding. The ACR response measure includes a level of acute phase

reactants, and in a novel therapy, which we're using, we see it as being beneficial, but we don't see any change in the level of acute phase reactants.

So this again causes you to question whether or not you're looking at the right sort of responders, particularly because novel therapy interventions are likely to change what we call our response and what we call lack of response.

There are many different test requirements if you're going to be using a reliable pharmacodynamic test. Many of these are analytical, but there are also practical issues. You basically want to test which isn't particularly invasive, which has where you get the information out of the test in a relatively short time, and certainly where the value of the test information outweighs the acquisition costs of that information.

Obviously availability of that test is also important. One practical aspect of using it is in many cases, some of the novel markers that we're looking at do not have widely distributed testing platforms established in the market, and this is basically going to be a hindrance to getting wide uptake of these sort of tests in the market.

There are also other considerations in terms of the predictive value of that test and the invasiveness. Certainly in our work we've seen that host genetic factors, it is quite easy to get information about host genetic factors based on pharmacogenetic tests, but there are limitations currently that we see with the predictive value of host genetic factors, principally because of the penetrance of many of the genetic factors that we're looking at.

Other host factors such as proteins, serum proteins, metabolites, and chemokines can be acquired out of blood tests, and infectious agent factors can also be acquired out of blood tests. Many tests that we would like to use require the use of tissue, and in many cases, it is very difficult. It's impractical to require a patient to give you a tissue sample in order to test for a predictive marker.

One exception to this is obviously in oncology where in many cases, one has access to samples from the primary tumor.

Obviously one also wants to look at the clinical utility of response prediction and trade off the risks and benefits related to an empiric approach, whether or not the response rate is, as I said, is closer to 100 percent or closer to zero percent, the relative predictive value, and issues related to market acceptance of practicality.

So in summary, some of the challenges around this are identifying the right biomarker early enough. I'll just go into in a couple of seconds some of the challenges around developing pharmacodiagnostic tests within drug time lines, and ensuring collection of enough of the right samples and defining the sampling conditions at the right time, storing the samples effectively, and also having a good protocol for the preparation of the test out of the test sample.

So I think if you have a validated biomarker, something where you know what the biological information coming out of that biomarker is and you have a good analytical test for that biomarker, essentially there are few issues to integrating this into a drug development. You basically just use the lab-validated diagnostic test during your pharma development, and you can use that in your filing together with the drug filing. This shouldn't be a big issue.

It becomes more of an issue if you identify the biomarker, let's say in late preclinical work, and you have to work up a biomarker assay yourself. Generally what you will do is you will develop

let's say a prototype assay, you'll then use this prototype assay during your drug development, and you'll try and then work up a commercial test for this, such that it can be introduced into the market, and you do a validation, a crossover validation between the commercial test and the assay in development, and hopefully you'll get good enough correlation that you can use this in a data file. So this is, I think this also works as long as you do the proprietary work in the right way.

It becomes more of a problem if you discover the biomarker either in late development or post-launch. One of the reasons is that you won't have a commercial IVD when you launch your drug, and the second reason is that you probably won't have been able to integrate this in your regulatory submission, and also your submission to pay your organizations, such that it won't be included in your pharmacoeconomic model.

This means that many issues arise when you run into this sort of situation. I'll go through some of those issues in a little while.

So I think one of the other things that we have to take into account about the incentives for pharma companies to do this is that all this work costs money, and pharma companies have to balance the investments that they make in biomarker work versus the investments they make in new medicines.

They'll do this as rational profit-incented organizations, they'll do this based on the incentives which are laid out in front of them.

So this basically summarizes what I've said, that in early development, pharmacodynamic and tox markers help, prognostic markers help, but in late development, we don't see many cases currently of therapy response markers which are predictive enough to allow us to recruit based on those. So this isn't simplifying the situation currently. It does not make drug development any cheaper, and it's not making drug development any simpler.

In few cases do we expect to be able to use surrogate markers in place of endpoints, but we expect that increased use of disease markers will allow us to run more effective and efficient trials, and to differentiate our compounds in the market more effectively. We expect that these activities will lead to the development of innovative diagnostics and improvements in the practice of medicine, and this will feed back into improved drug development with time.

So I think I've been through most of the points on this slide. What I want to go onto is the impact of pharmacodynamics on key pharma value drivers. The value drivers that we see in drug development are basically the quantity of clinical candidates, new molecules which we can put into a pipeline. Here we essentially see that the impact of pharmacodynamics is mutual.

The quality of molecules which you have in the pipeline, and this is essentially measured in terms of success or attrition rates, and here we see us being able to improve the potential of getting a specific molecule out of the end of the pipeline by using pharmacodiagnostic tests simply because there are some tests which we'll be able to bring to market which we would otherwise not have been able to do.

Time also is another important value driver. This is the dwell time of a project or phase, and we see this as negative, because it takes time to integrate these tests, to interpret these tests, so this is going to be a negative impact on time. The overall cost per clinical compound brought into discovery will also probably be negative. It might not be very negative, but it will likely be

negative. We think that the overall impact on project value for a successful project is likely to be positive.

So taking this all together, adding predictive pharmacodiagnostics to drug development adds cost, uncertainty, complexity, and the potential for value creation currently varies from project to project, and one has to make a project-specific decision.

If you think in terms of, this is just in terms of attrition rates, I think they might not apply to all pharma companies, but this is I think illustrative of the current situation. You have roughly a chance of somewhere between I guess 3 in 100 and 10 in 100 of drugs which you put in at the front end of your development pipeline coming out of the back end of the pipeline.

One of the goals of pharma companies currently is to reduce late phase attrition, principally because the cost per project increased significantly the later the phase. So I think one of the challenges we see with this work is if you are going to do this effectively, you basically have to integrate biomarker work with all the programs you have early in the pipeline, and that only a very few of these are going to be successful.

So all that work that you put in early in the pipeline adds additional cost, and you're not seeing any benefit in terms of the specific projects, or you are basically losing something like 95 percent of those biomarker projects because the drug isn't getting to market.

So this attrition rate that you have for drugs also applies to your biomarker projects. One of the important things that companies are trying to do is they are trying to capitalize broadly upon their investments in biomarker work by applying these throughout or to other compounds in a particular therapeutic area.

This chart is deliberately complicated, but it basically shows what the effects of pharmacogenetics and pharmacodiagnostics are on pharma value flows. You can see there are many different factors, which one has to take into consideration, and these have to be balanced off against one another.

You have major factors, minor factors, factors which some are positive, some are negative. I think this shows the complexity from applying these on a specific project in determining whether or not you are likely to get a positive value or a negative value by integrating biomarker work into your pharma development project.

So the economic rationale for personalized meds, and I think this is clear to pharma companies, that there is a clear economic rationale, particularly from a societal perspective, that if you have targeted therapies where a drug is linked to a pharmacodiagnostic, non responders or poor responders are removed from the pool of users, and monetary and negative utility for adverse events are avoided.

Better targeting can lead to a greater volume of adoption by good responders, some of whom would not have used the drug previously, or may have discontinued use of the drug previously, and good responders may have improved compliance, and therefore, additional net benefits.

So the improvement of predictability of outcomes create additional value for patients as they essentially face less uncertainty. I think these economic rationale are very clear to pharma companies.

What is the value? This is just looking at innovative medicine in general. This is what very unspecific but obviously fully informed patients are willing to pay. We see the value as what patients are willing to pay based on these various benefits. So this is the value of innovation for novel drugs is what patients are willing to pay, broad societal value, and then obviously there is an innovative perspective. So how are the incentives aligned with working in this area.

So the personalized medicine, the economic value proposition to patients, as I say of a personalized medicine or targeted medicine, is to decrease the cost of adverse events, faster and more complete adoption, and hopefully improve compliance and greater predictability of outcome.

I just want to go through an example for you to illustrate this. If we look at a new drug which has a 20 percent response rate, this is towards the lower end of that scale I showed you earlier on, the company who is developing this has an initial price estimate that they can charge \$1,000 per year for this drug, what our patient or payer is willing to pay for this, how much it is worth if you know who will respond and who won't, so what's the value of the reduction in the certainty, and what are the side effects.

So again, taking this example, if you have for this new drug a response prediction test, and this is I think, again, we have to see that this is entirely theoretical, because we're saying that we have a test which with 100 percent sensitivity and 100 percent specificity, accurately predicts the response to this new drug. We know that is entirely theoretical.

It is based on a readily detectable biomarker. So if we were to screen all potential patients and only treat those likely to respond, what would be the value of this? So it is clear to see what we expect to see happen here, that we would get a targeted indication. We would hopefully get based on who is responding and who doesn't respond, faster uptake, and improved competitive position. So what should the price be?

So with no test, we have, if you're looking at 1,000 patients and patients are willing to pay \$1,000 per patient per year without the test, then the value would be 1,000 times \$1,000, \$1 million for the company who is selling this.

Now, if we have a perfect test, we have 200 patients, one could posit that the willingness of each specific patient to pay would go up six times because they don't have a 1 in 6 chance of responding, or a 1 in 5 chance, they have higher than that, and the incremental value that we see here over and above the situation without the test essentially comes from what we see as an additional value in reducing the uncertainty.

This reduction in uncertainty has a value over and above the case where one has to take a chance. So this lays out what we see as the potential value for this. Now, this, as I said, this is a theoretical case, but we believe the underlying concepts which we built into this case are broadly applicable. One can always argue about what the incremental value of the certainty is, but we certainly see that there is value attached to that.

Now, a lot of the value capture that goes on, that depends on the manufacturer's ability to set price. This comes into then the economic incentives of companies to do this. So if the pharmaceutical manufacturer cannot modulate its price, then what it essentially gets out of it, even with the reduced uncertainty, is it only gets \$200,000 instead of \$1 million.

Who captures the other value? Basically payers and patients capture the rest of the value in this story. So this really I think illustrates very clearly the impact of timing upon the implementation of a stratifying test in drug development. The price is nearly always set with novel drugs quite early in the drug's life, essentially immediately after registration or around registration.

This shows if one isn't able to adjust price, which is I think generally the case today, the company who is manufacturing this and who is disincented essentially from discovering and applying a stratifier, although the total value for society stays roughly the same, or perhaps increases with this reduction in certainty. So I think this is one very important factor to look at, is currently there are disincentives for pharma companies to do this sort of work post initial fixing of the price.

What about diagnostic companies? There certainly seems to be some incentives for diagnostic companies to do this sort of work. If you think about the potential diagnostics, if they were able to capture the rest of this value, then there would be very big incentives for them to do this work, because they'd be able to charge money for the test.

However, current reimbursement schemes for diagnostics do not reward for value creation. They are essentially technical reimbursement schemes, and this supply is around the world. This isn't just the United States which has this situation. So there are I think insufficient incentives in many cases for diagnostic companies to invest in this, particularly when we look at the attrition equation which I showed you earlier on.

If you are going to invest in predictive markers and you're trying to look at hundreds of potential medicines, which ones do you invest in, and how do you deal with the attrition of all of those projects which never get to market? So this, again, underlines the fact that there are really not all that many incentives in place for diagnostic companies to do this work in a systematic way, and this is essentially because of the loss of value which comes out of this, because they are not able to get reimbursement based on the value that they create.

So as I say, the capturing of the value depends on pricing and reimbursement conditions, obviously intellectual property plays a role, competition, and timing plays a role.

So the key messages out of this are the value capture of a linked diagnostic/therapeutic depends on many factors, including pricing, reimbursement, intellectual property, competitive market conditions, and the specific characteristics of diagnostic and therapeutic.

Along with the scientific and clinical considerations, whether, when, and how this value was created, we believe is inextricably related to who captures it. So unless you have a stronger correlation of value capture and value creation, those disincentives will remain. Our view is that it would be wise to encourage value-based flexible pricing in reimbursement systems to provide a level playing field that together with intellectual property protection appropriately rewards diagnostic and therapeutic innovation.

This is a summary of those points. I don't think I have to go through it in any great detail, because I think I've teased out the main points already.

I just want to acknowledge a number of colleagues within Roche. Lou Garrison has cooperated with this in terms of putting this model together, from the University of Washington, and to some colleagues at Genentech and Boston Consulting Group as well. Thank you very much for your attention.

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DR. WINN-DEEN: Thanks very much, Tom.